EP03/09151

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P01/7700 0.00-0219152.6

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1. Your reference — RFW/JD/B45319

2. Patent application number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89, B-1330 Rixensart, , Belgium

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Belgian

81927001

4. Title of the invention — Novel device

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

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GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* — 79608220003

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Continuation sheets of this form	10
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Claim(s)	DMC
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Priority Documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
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11. We request the grant of a patent on the basis of this application

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12. Name and daytime telephone number of person to contact in the United Kingdom: R F Walker 020 80474485

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Novel Device

This invention relates to a novel device, being a closure system for vials, particularly for pharmaceutical vials, i.e. for the sterile containment of drug substance or vaccine products therein.

Drug substance and vaccine products are frequently provided in vials which are closed with an elastomeric closure part through which a hollow needle can be passed, punching the closure part, and via which the drug substance or vaccine product may be extracted for use, optionally after reconstitution by an aqueous medium introduced into the vial via the needle. Normally such a vial has a mouth opening bounded by a flange-shaped rim, and the closure part is held in a closing relationship with the mouth opening by a flexible metal clamp part which surrounds the perimeter of the closure part and holds it tightly against the rim. Often a central area of the closure part may be punctured by the needle, and the clamp part has a removable central part, which prior to use covers this central area of the closure part, and which can be removed immediately before use. Often this central part is connected to peripheral parts of the clamp part by thin frangible links, enabling the central part to be initially connected to the peripheral parts and detached prior to use, giving tamper evidence. A problem with this known device is that it is difficult to achieve a sterile seal between the central part and closure part, so the user has to "sanitise" the central area of the closure part immediately prior to use, e.g. using an alcohol wipe.

It is also known, e.g. from US-A-2002/0023409, to provide a pharmaceutical vial having a closure part made of thermoplastic material. Such a vial can be filled using a hollow needle passed through the closure part, the needle is then withdrawn, and the small residual puncture hole may then be sealed by heat sealing, e.g. using a focussed laser beam.

It is an object of the present invention to provide a vial closure system which in part at least overcomes the above-mentioned problems of known closure systems, and is particularly suited to vial closures which can be heat-sealed after filling using a hollow needle, as described above. Other objects and advantages of the present invention will be apparent from the following description.

According to this invention, a closure system is provided for a vial of the type having an upwardly-facing mouth opening bounded by a rim, the closure system comprising:

an elastomeric closure part shaped to sealingly engage with the mouth opening, having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle,

a clamp part able to engage with the vial, particularly with the rim of the mouth opening, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening;

the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial,

a cover part, engageable with the clamp part and/or the vial to cover the said region of the closure part, a lower surface of the cover part facing the upper surface of the closure part when so engaged and having a sealing ridge projecting therefrom to a sealing edge that follows a closed perimeter, so that when the cover part is engaged with the clamp part and/or the vial the sealing edge engages with the closure part to form an enclosure with the closure part, at least that part of the cover part which includes the sealing ridge being removable from engagement with the clamp part and/or the vial.

The terms "upward", "upper", "lower" etc. and derived directional terms are based on the normal configuration of a vial in a vertical orientation with the mouth uppermost, but of course are applicable to any orientation of the vial and the parts of the closure system.

The vial is preferably of the type having a neck immediately downward of the mouth opening, and having a rim in the form of a flange having upper and lower surfaces extending transverse to, preferably perpendicular to, the upper-lower axis. Such vials are well known in the pharmaceutical industry. Suitably the upper surface of the flange may be bounded by a peripheral upwardly-extending kerb edge. Suitably the upper surface of the flange may have an upwardly extending sealing ridge to engage against a downward facing surface of the closure part to improve sealing between the closure part and the flange. The vial may be made of

glass, or of a hard plastic material accepted for use in the pharmaceutical industry. An example of such a plastics material is the cyclolefin copolymer "Topas" made by Celanese Corporation.

The closure part preferably has a downwardly extending plug part which fits into the mouth opening of the vial, and an outwardly extending peripheral flange part, a downward facing surface of which can engage with the upward facing surface of a rim of the vial mouth opening in the form of a flange. Suitably the plug part has an outer perimeter which fits conformingly within the kerb of the flange. Upwardly of such a flange part the closure part may be flat but is preferably upwardly convex, e.g. domed or of a (frusto) conical shape. The plug part is suitably of a hollow cylindrical shape with an upper end of the hollow cylindrical interior extending into this upper domed or conical part.

Preferably at least the upper surface of the closure part adjacent to the said region, preferably an upper part, preferably the whole of the closure part is made of a thermoplastic elastomer material, so that a puncture hole formed as a result of filling the vial using a hollow needle may be sealed by thermal sealing, e.g. using a laser as described in US-A-2002.0023409. A suitable thermoplastic elastomer material is a 50:50 w:w blend of the polymers "Engage" supplied by Dupont-Dow, and "Dynaflex" formerly known as "Kraton" as supplied by Shell but now available from GLS (USA) who supply this blend, and including a dye, e.g. grey, to enhance absorption of laser light so that the elastomer material may be heated using laser light. Under irradiation from a focussed 980nm laser this polymer easily fuses at ca. 180°C and sets on cooling.

The clamp part is preferably made of a mouldable plastics material, and is able to engage with the vial, preferably being engageable with the above-mentioned flange around the rim, for example by a snap-fit engagement underneath a downwardly facing surface of such a flange part. The clamp part preferably comprises an upper wall part having the aperture therein, preferably a central aperture, with peripheral skirt walls extending downwardly therefrom and having snap-fit engagement parts thereon to engage with the vial, e.g. with the said flange.

If the closure part has the above mentioned upwardly convex shape, then preferably the upper wall and the upwardly convex part of the closure part are

profiled such that the upwardly convex part bulges above the adjacent upper surface of the upper wall. Preferably the upper surface and the upwardly convex part may be profiled to form a smooth convex shape.

The cover part is preferably engageable with the clamp part. For example the cover part may be engageable by snap-fit means with the upper wall, or skirt wall of the clamp part, or the junction between the upper wall and skirt wall. For example the cover part may comprise a cap having an upper wall and a peripheral skirt wall, and the skirt wall of such a cap may have a snap-fit engagement part adjacent its lower extremity, to engage with the clamp part. Such snap-fit means may comprise a ridge on the cover part and a corresponding groove on the clamp part, or vice versa.

The cover part preferably at least partly covers a central aperture in the clamp part to thereby cover the above-mentioned region of the closure part. The sealing ridge extends downwardly from the lower surface of the upper wall of the cover part which is adjacent to and above the closure part when the cover part is engaged with the clamp part. The sealing edge preferably has a generally triangular section as cut parallel to the up-down direction, so that the sealing edge comprises the apex of the triangle. The sealing edge preferably follows a ring-shaped, e.g. circular, oval or polygonal closed perimeter as viewed looking upwardly toward the lower surface of the upper wall of the cover part.

The part of the cover part which includes the sealing ridge is preferably made removable from the clamp part and/or vial as follows. Preferably the upper wall has a segment, e.g. a pie-slice segment of a generally circular upper wall, linked to the remainder of the upper wall and/or skirt wall by one or more thin, frangible link which can easily be severed to allow the segment to be sufficiently (partly or wholly) detached from the remainder of the cover part.

Suitably the cover part may be made by injection moulding of a plastics material, suitably of the same plastics material as the clamp part.

The present invention further provides a vial when fitted with a closure system as described herein.

The present invention also provides a method of filling a vial comprising:

providing an assembly of an empty vial having a closure part and clamp part thereon;

inserting a filling needle downwardly through the upper wall of the closure part;

injecting a liquid medicament through the filling needle to fill the vial to a suitable extent;

withdrawing the needle to leave a residual puncture hole;

engaging a cover part with the clamp part.

Preferably prior to engaging the cover part a laser beam or other source of heat is directed at that part of the upper surface of the closure part where the puncture has occurred to melt the elastomer material in the immediate locality of the puncture, and to thereby seal the residual puncture hole.

The above-mentioned assembly may be supplied from a separate source, so as a further aspect this invention provides a pharmaceutical vial having a mouth opening closed by an elastomeric closure part shaped to sealingly engage with the mouth opening and having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle, a clamp part engaged with the rim of the mouth opening, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial, the clamp part and/or vial being engageable with an at least partly removable cover part able to cover the said region of the closure part and being able to form an enclosure with the closure part.

The invention will now be illustrated by way of example only with reference to the following drawings.

Fig. 1 shows a longitudinal section of a vial and vial closure system according to this invention cut along an up-down plane.

Fig. 2 shows a cover part of a closure system according to this invention viewed in various orientations.

Fig. 3 shows a perspective view of a vial having a closure part and a clamp part in place,

Fig. 4 shows a perspective view of the vial plus closure part and clamp part as shown in Fig. 3, with a cover part also in place.

Fig. 5 shows the vial plus closure part, clamp part and cover part of Fig. 4, with the cover part partly removed.

Fig. 6 shows a longitudinal section of a partly assembled vial and closure system of this invention.

10 vial

11 mouth opening

12 neck

13 rim, 13A upper surface, 13B lower surface

14 peripheral kerb 14

15 sealing ridge

20 closure part

21 plug part, 21A interior of the plug part

22 outwardly extending flange

23 upper part of the closure part

24 upper wall, 24A central region

30 clamp part

31 upper wall

32 skirt wall

33 snap fit engagement parts

34 upper downward facing surface

35 lower downward facing surface

36 central circular aperture

37 groove

40 cover part

41 upper wall.

42 peripheral skirt wall

43 snap fit engagement parts

44 sealing ridge

45 sealed enclosure

46 removable segment of the upper wall and skirt wall of the cover part

47 thin severable links

50 ring-shaped stand

Referring to Fig. 1 a vial 10 is shown being of generally cylindrical shape. At its upper end as shown the vial has a mouth opening 11, with a neck 12 immediately below. Larger capacity vials 10 may have a wider body section below their neck 12, as is well known in the art. The mouth opening 11 is surrounded by an outwardly extending rim 13 in the form of a flange having an upper surface 13A and a lower surface 13B. The upper surface 13A of flange B is bounded by a peripheral kerb 14. From upper surface 13A of flange 13 a sealing ridge 15 extends upwardly being of generally triangular section as cut along an up-down plane and of circular ring shape concentric with the cylindrical vial 10 in plan. The upper inner edge of the neck 12 is of a conical profile flaring upwardly, to guide the insertion of the plug part 21 (to be described) of the closure part 20.

Inserted into mouth opening 11 and extending some way down neck 12 is the plug part 21 of a closure part 20 made integrally of a thermoplastic elastomer material. The plug part 21 is a tight fit into the neck 12 to thereby form a close seal. The closure part 20 has an outwardly extending flange 22, of shape and dimensions such that flange 22 fits comfortably within kerb 14. The flange 22 has an upper surface and a lower surface. When the closure 20 is in position as shown in Fig. 1 the lower surface fits against the upper surface 13A of flange 13 and the sealing ridge 15 compresses and deforms the elastomer material of the lower surface of flange 22, contributing to a good seal between surfaces 13A and the lower surface of flange 22.

The plug part 21 is of generally cylindrical shape and has a hollow interior 21A. The upper part 23 of the closure part 20, centrally inward of flange 22 is upwardly convex, being of a frusto-conical shape having a flat upper surface. The upper part of the interior 21A of the plug part generally follows the upward convex shape of the upper part 23. The upper end of the cylindrical interior 21A is closed by an upper wall 24 which is thin enough to be punctured by a hollow needle (not shown) by which the vial 10 can be filled whilst the closure part 20 is in place.

A clamp part 30 holds the closure part 20 in place against the flange 13. The clamp part 30 comprises an upper wall 31 generally circular in plan, from the

periphery of which downwardly extends a skirt wall 32. At the lower extremity of the skirt wall 32 is a snap fit engagement part 33, being a wedge shaped inwardly extending lip which can engage under the lower surface 13B of flange 13 to hold the clamp part 30 in place on the assembly of vial 10 and closure part 20. The clamp part 30 is made of a resilient plastics material to facilitate this. The clamp part 30 has two regions of downward facing surfaces, being an upper downward facing surface 34 and a lower downward facing surface 35 which bear respectively upon the upper surface of the upper wall 24 of the closure part 20 and upon the upper surface of the flange 22 to hold closure part 20 in place against flange 22.

In the upper wall 31 of the clamp part 30 is a central circular aperture 36, through which bulges the central convex part of the upper part 23 of closure part 20 so that a central region 24A of the upper wall 24 is exposed through the aperture 36. The profile of the upper surface of the clamp part is profiled so that the upper part 23 of closure part 20 projects in this way. The inner perimeter of the aperture 36, adjacent to the upper downward facing surface 24, is also shaped to correspond with the outer profile of the upper part 23 of the closure part 20.

Around the periphery of the upper wall 31 of the clamp part 30 is a groove 37 with which the cover part 40 engages.

The cover part 40 is in the form of a cap comprising an upper wall 41, with a peripheral skirt wall 42, at the lower extremity of which is a snap fit engagement part 43 being an inwardly directed wedge shaped lip, which can engage with the groove 37 on clamp part 30 to retain cover part 40 securely in place on clamp part 30. The cover part 40 is made of a resilient plastic material to facilitate this.

A lower surface of the upper wall 41 has a sealing ridge 44 extending downwardly therefrom. As seen looking upwards toward the lower surface this ridge 44 has a circular ring-shaped plan and is of a triangular section so that it terminates in a lower knife edge. As the cover part 40 is held in contact with the clamp part 30 by the snap-fit parts 43, 37 its resilience forces it against the central region 23A of the upper part 23 of the closure 20, and the ridge 44 engages with and compressibly deforms the elastomer of the central region 23A to thereby form a seal with the region 23A. A sealed enclosure 45 is thereby formed between the cover part 40 and the closure part 20. The seal between the ridge 44 and the region

23A is sufficient that contaminants such as microorganisms, virus particles etc cannot pass the seal, so the enclosure 45 can remain sterile.

Figs. 2A-2E respectively show a plan view, a side view looking in the upward direction of Fig. 2A, and three perspective views of the cover part 40. As seen more clearly in Figs. 2, 3 and 4, whereas the lower part of the skirt wall 42 and its lip 43 extend in a continuous ring, a part 46 of the upper wall 41 of the cover part 40, including that part of the upper wall 41 which has the sealing ridge 44 on its lower surface, is made as a segment which is connected to the remainder of the cover part 40 by thin severable links 47, being integrally made bridges of plastics material. The peripheral edge of this segment 46 may be lifted by a user as shown to thereby break the bridges 47, and to lift the segment 46 from the closure part 20. This breaks the seal between the ridge 44 and the central region 24A of the upper wall 24 of the closure part 20 and exposes the central region 43A, leaving the cover part 40 retained on the clamp part 30 by the snap fit lip 43 of skirt wall 42.

The vial 10 and closure system 20, 30, 40 may be used as follows. An assembly of an empty vial 10, closure part 20 and clamp part 30 is provided as shown in Fig. 6. This assembly may be sterilised by appropriate generally known methods either before (i.e. as separate parts) or after assembly. In a sterile environment such as a flow of sterile air, a filling needle (not shown) may then be inserted downwardly through the upper wall 24 of the closure part 20, and a liquid medicament injected therethrough to fill the vial 10 to a suitable extent. Known filling needles suitable for this purpose may also have an air exit channel to release displaced air from the interior of vial 10. When the vial 10 has been filled in this manner the needle is withdrawn. The elastomer material of the wall 24 closes around the residual puncture hole (not shown) in closure part 20, and whilst still in the sterile environment a laser beam or other source of heat is directed at that part of the upper surface of the wall 24 where the puncture has occurred to melt the elastomer material in the immediate locality of the puncture, and to thereby seal the residual puncture hole. Then, still in the sterile environment, the cover part 40 may be engaged with the clamp part as shown in Fig. 1.

Immediately prior to use of the medicament the segment 46 is lifted as described above, and an injection needle attached to a syringe (not shown) may be

inserted through the central region 24A, in the normal manner of using a vial closed with an elastomeric closure.

Because the central region 24A has been maintained in the sterile enclosure 45 until the segment 46 is lifted, there is no need for the user to give the region of the closure part 20 to be punctured, i.e. the region 24A, a wipe with a sanitising agent as would be necessary with prior art vial closure systems.

Figs. 1-6 show a relatively small capacity vial 10 of an overall cylindrical profile. For stability and to assist automated handling the base 10A of the vial 10 is mounted in a ring-shaped stand 50 extending outwardly from the overall cylindrical shape of the vial 10 at its base.

Claims.

1. A closure system for a vial of the type having an upwardly-facing mouth opening bounded by a rim, the closure system comprising:

an elastomeric closure part shaped to sealingly engage with the mouth opening, having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle,

a clamp part able to engage with the vial, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial,

a cover part, engageable with the clamp part and/or the vial to cover the said region of the closure part, a lower surface of the cover part facing the upper surface of the closure part when so engaged and having a sealing ridge projecting therefrom to a sealing edge that follows a closed perimeter, so that when the cover part is engaged with the clamp part and/or the vial the sealing edge engages with the closure part to form an enclosure with the closure part, at least that part of the cover part which includes the sealing ridge being removable from engagement with the clamp part and/or the vial.

2. A closure system according to claim 1 having a downwardly extending plug part which can fit into the mouth opening of the vial, and an outwardly extending peripheral flange part, a downward facing surface of which can engage with the upward facing surface of a rim of the vial mouth opening in the form of a flange.

3. A closure system according to claim 2 wherein upwardly of the flange part the closure part is upwardly convex.

4. A closure system according to claim 1, 2 or 3 wherein at least the upper surface of the closure part adjacent to the said region is made of a thermoplastic

elastomer material, so that a puncture hole formed as a result of filling the vial using a hollow needle may be sealed by thermal sealing.

5. A closure system according to any one of the preceding claims wherein the clamp part is made of a mouldable plastics material, and is engageable with the above-mentioned rim bounding the mouth opening of the vial.

6. A closure system according to any one of the preceding claims wherein the clamp part comprises an upper wall part having the aperture therein, with peripheral skirt walls extending downwardly therefrom and having snap-fit engagement parts thereon to engage with the vial.

7. A closure system according to claim 6 wherein the closure part has an upwardly convex shape, and the upper wall and the upwardly convex part of the closure part are profiled such that the upwardly convex part bulges above the adjacent upper surface of the upper wall.

8. A closure system according to any one of the preceding claims, wherein the cover part is engageable with the clamp part.

9. A closure system according to claim 8 wherein the cover part is engageable by snap-fit means with the upper wall, or skirt wall of the clamp part, or the junction between the upper wall and skirt wall, of the clamp part.

10. A closure system according to any one of the preceding claims wherein the cover part comprises a cap having an upper wall and a peripheral skirt wall, and the skirt wall of such a cap has a snap-fit engagement part adjacent its lower extremity, to engage with the clamp part.

11. A closure system according to any one of the preceding claims wherein the cover part covers a central aperture in the clamp part to thereby cover the above-mentioned region of the closure part.

12. A closure system according to any one of the preceding claims wherein the sealing edge has a generally triangular section as cut parallel to the up-down direction, so that the sealing edge comprises the apex of the triangle.

13. A closure system according to any one of the preceding claims wherein the sealing edge follows a ring-shaped perimeter as viewed looking upwardly toward the lower surface of the upper wall of the cover part.

14. A closure system according to any one of the preceding claims wherein the upper wall of the cover part has a segment linked to the remainder of the upper wall and/or skirt wall of the cover part by one or more thin, frangible link which can easily be severed to allow the segment to be at least partly detached from the remainder of the cover part.

15. A pharmaceutical vial having a mouth opening closed by a closure system according to any one of the preceding claims.

16. A pharmaceutical vial having:

a mouth opening closed by an elastomeric closure part shaped to sealingly engage with the mouth opening and having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle,

a clamp part engaged with the rim of the mouth opening, and able to bear upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial,

the clamp part and/or vial being engageable with an at least partly removable cover part able to cover the said region of the closure part and being able to form an enclosure with the closure part.

17. A pharmaceutical vial according to claim 15 or 16 wherein the vial has a neck immediately downward of the mouth opening, and has a rim in the form of a flange having upper and lower surfaces extending transverse to the upper-lower axis.

18. A method of filling a pharmaceutical vial, comprising the steps of:

providing an assembly of an empty vial having an elastomeric closure part shaped to sealingly engage with the mouth opening and having a lower surface facing the interior of the vial and an opposite upper surface facing away from the vial, and capable of being punctured by a needle, and a clamp part engaged with the vial, and bearing upon the upper surface of the closure part to hold the closure part in a closing relationship with the mouth opening, the clamp part having an aperture therein through which a region of the upper surface of the closure part is exposed when the clamp part is engaged with the vial;

inserting a filling needle downwardly through the upper wall of the closure part;

injecting a liquid medicament through the filling needle to fill the vial to a suitable extent;

withdrawing the needle to leave a residual puncture hole;

engaging a cover part with the clamp part and/or the vial to cover the said region of the closure part, a lower surface of the cover part facing the upper surface of the closure part when so engaged and having a sealing ridge projecting therefrom to a sealing edge that follows a closed perimeter, so that when the cover part is engaged with the clamp part and/or the vial the sealing edge engages with the closure part to form an enclosure with the closure part, at least that part of the cover part which includes the sealing ridge being removable from engagement with the clamp part and/or the vial.with the clamp part.

19. A method according to claim 18 wherein prior to engaging the said cover part a laser beam or other source of heat is directed at that part of the upper surface of the closure part where the puncture has occurred to melt the elastomeric material

in the immediate locality of the puncture, and to thereby seal the residual puncture hole.

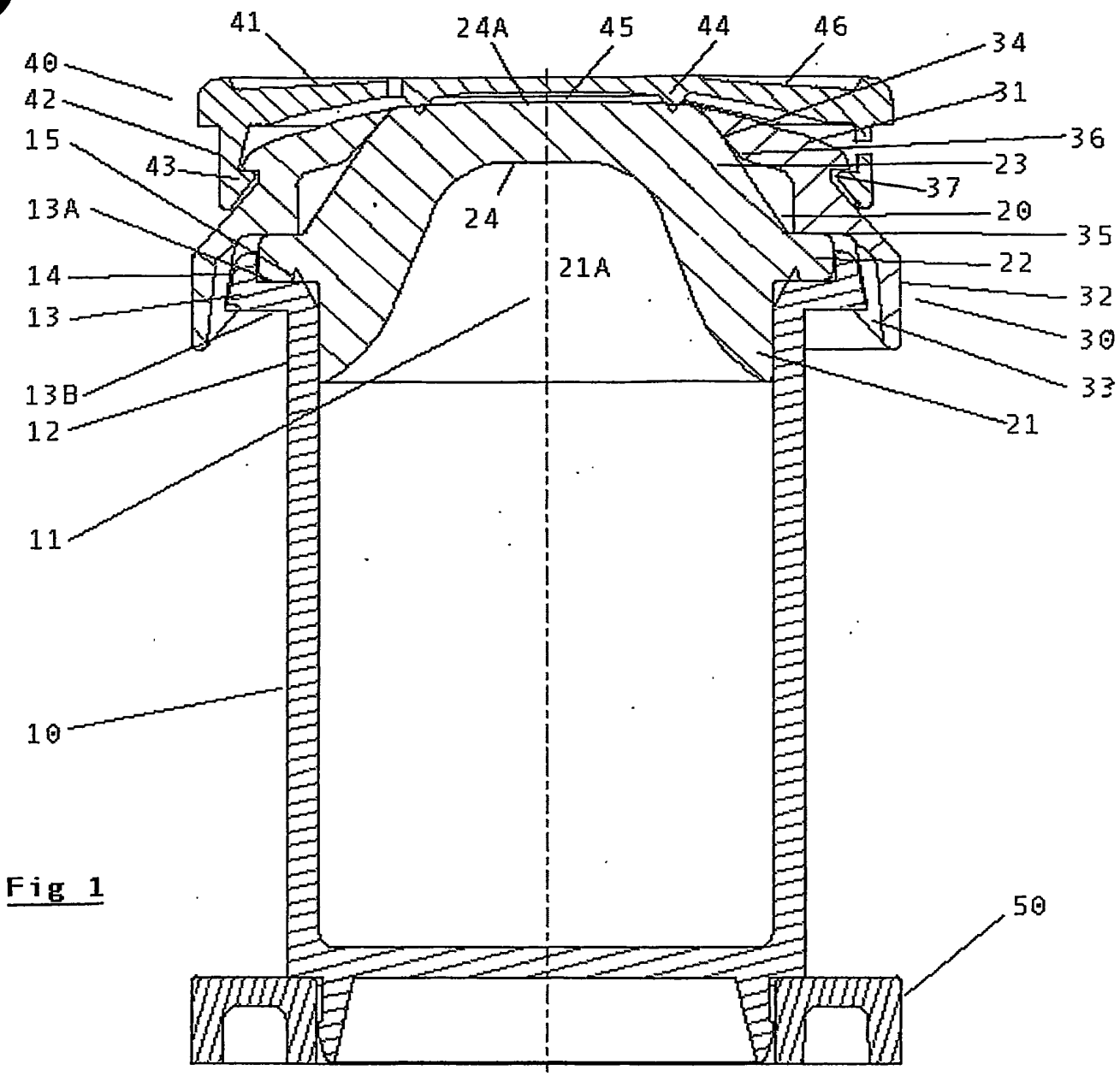
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Fig 1

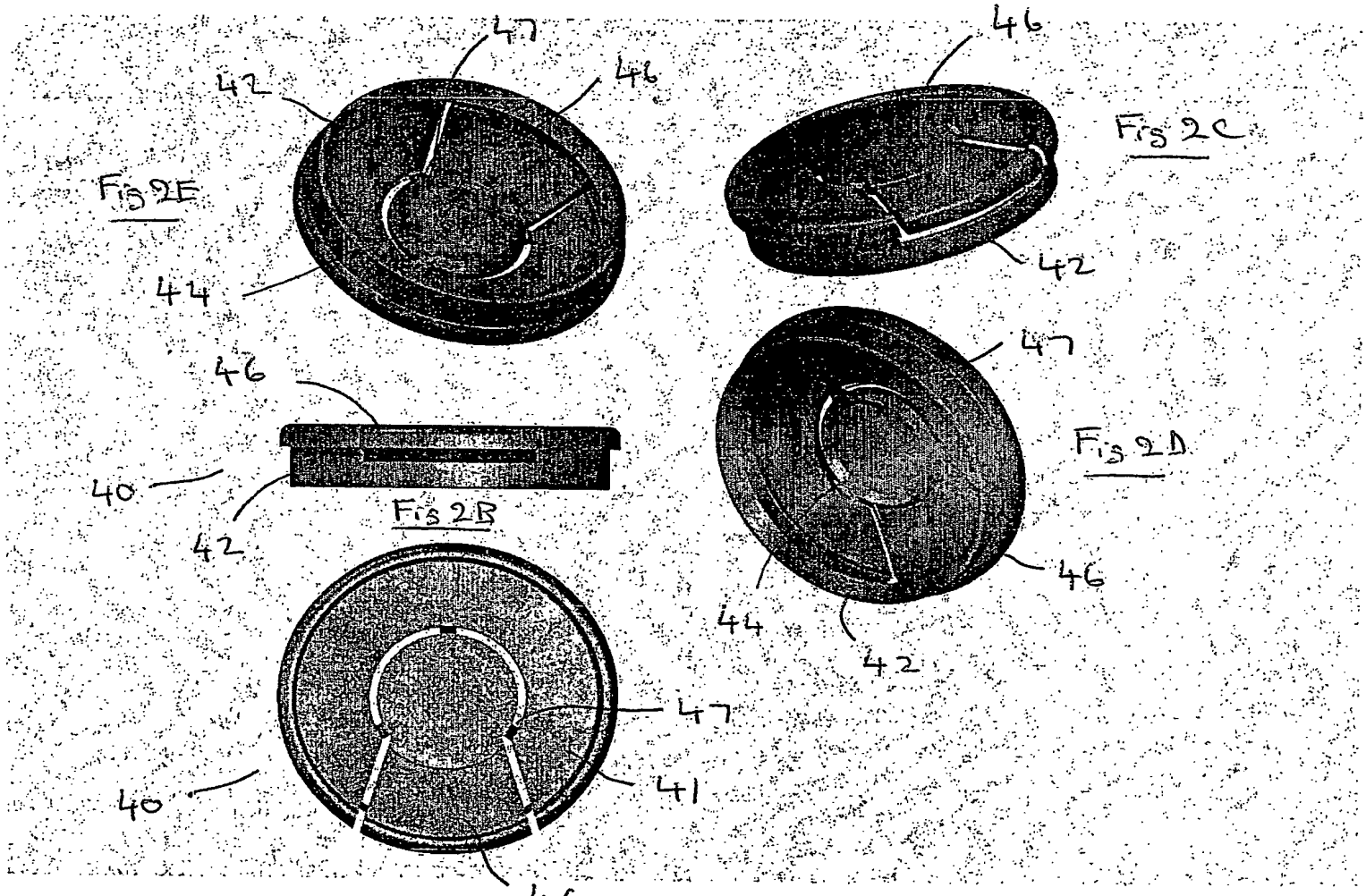

Fig 2E

Fig 2C

Fig 2D

Fig 2B

Fig 2A

Fig. 2

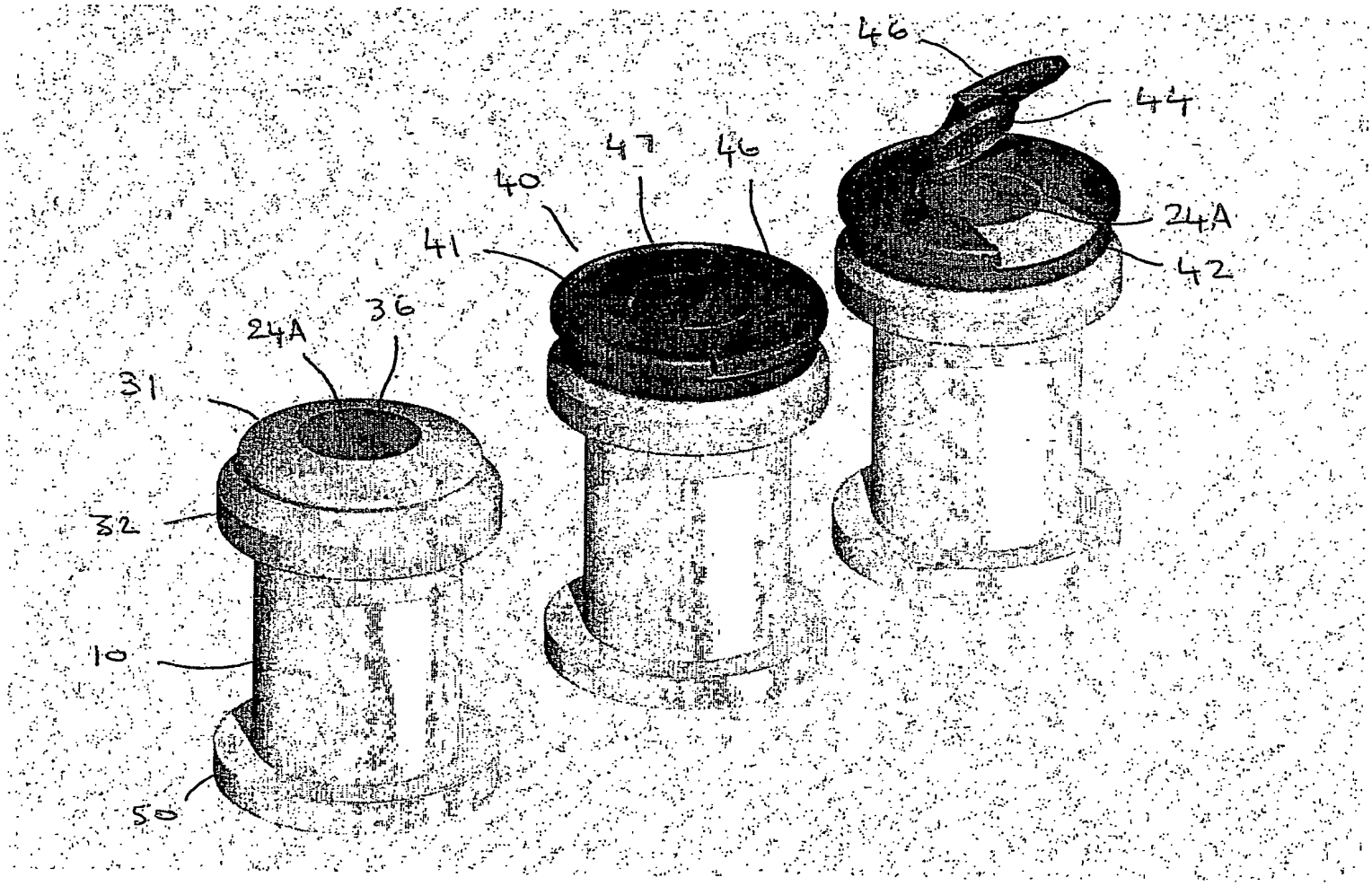

Fig. 3 Fig. 4 Fig. 5

Fig 6